REMARKS

Claim Rejections Under 35 U.S.C. § 103(a)

I. Claims 1, 3-10, 14, 17, 24, and 27 are Patentable over Madsen *et al.*, Callewaert *et al.*, and Jensen *et al.*

Claims 1, 3-10, 14, 17, 24, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* (WO 98/10079) ("Madsen *et al.*) in view of Callewaert *et al.* (February 2000) "Bacteriocin Production with *Lactobacillus amylovorus* DCE 471 Is Improved and Stabilized by Fed-Batch Fermentation." Applied and Environmental Microbiology **66**(2): 606-613 ("Callewaert *et al.*) and Jensen *et al.* (1993) "Minimal Requirements for Exponential Growth of *Lactococcus lactis*." Applied and Environmental Microbiology **59**(12): 4363-4366 ("Jensen *et al.*"). Office Action at 2-4.

The Office Action asserts that Madsen *et al.* discloses a method of producing a heterologous polypeptide in a recombinant lactic acid bacterium which includes a nucleotide sequence coding for the polypeptide and, operably linked thereto, appropriate regulatory nucleic sequences to control expression of the coding sequence. It was asserted that the method comprises cultivating the bacterium under fed-batch cultivation. Office Action at 3. The Office Action noted that the differences between the reference and the claims are the media components, including glucose and controlled feeding of glucose, in fed-batch or continuous cultivation. To fill this gap, the Office Action asserts that Callewaert *et al.* discloses the growth of lactic acid bacteria in fed-batch fermentation with controlled feeding of glucose to maximize protein production and Jensen *et al.* discloses the minimal growth medium necessary for *Lactococcus lactis* bacterium, including genetically engineered strains, which comprises glucose and the components of claims 24 and 27. Office Action at 3. It was also asserted that the, "...reference discloses that the concentrations of the components of the medium, including glucose, could be increased." Id. at 4.

The Office Action concluded that one of ordinary skill in the art would have found it obvious to modify Madsen *et al.*'s growth medium used for lactic acid bacteria, by using the growth medium and techniques of Callewaert *et al.* and Jensen *et al.* Id. at 4.

Applicants respectfully traverse this rejection. Applicants enclose herewith a Declaration under 37 C.F.R. § 1.132 of Dr. Søren Michael Madsen ("Declaration"), to which they will refer in these remarks.

A proper obviousness rejection of patent application claims under 35 U.S.C. § 103(a) requires a showing by the United States Patent and Trademark Office ("PTO") that the invention defined in the rejected claim(s) as a whole is obvious in view of one reference or a combination of the references. Manual of Patent Examining Procedure (M.P.E.P.) at § 2142. Three basic criteria must be met to support a *prima facie* case of obviousness: (a) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference(s) teachings; (b) there must be a reasonable expectation of success; and (c) the prior art reference (or references when combined) must teach or suggest all the claim features. M.P.E.P. at § 2143.

The references cited in the Office Action do not individually or in combination suggest to a person of ordinary skill in the art the invention of the Applicants' claim 1 or the remaining claims subject to this rejection. Madsen *et al.* describes batch cultivation of recombinant lactic acid bacterial host cells for several uses, e.g., the manufacture of lactic acid bacterial starter cultures. See page 7 and Example 11. The cells comprise a particular expression vector, including a particular promoter sequence element described by Madsen *et al.* See page 6. However, contrary to the assertion in the Office Action, Madsen *et al.* does not teach fed-batch cultivation systems. See, e.g., Declaration at ¶¶ 25, 26. If Applicants overlooked the teaching by Madsen *et al.* of fed-batch cultivation conditions, they would appreciate the identification in Madsen *et al.* of the particular passage or passages containing such teaching. Madsen *et al.* also fails to teach or suggest continuous cultivation conditions. Id.

Callewaert *et al.* discloses the use of fed-batch cultivation to produce amylovorin L471, an endogenous protein which is a hydrophobic bacteriocin, produced by *Lactobacillus amylovorus* DCE 471, a strain of a naturally occurring bacterium. See page 606. Callewaert *et al.* also states that results of fed-batch fermentation are "...interesting regarding the development of continuous fermentation processes." See page 612. However, both Callewaert *et al.*'s teachings of fed-batch cultivation and comments on continuous cultivation were, "...to improve and stabilize the [particular] bacteriocin production." Id. at 606, 612; Declaration at ¶ 32. Thus, Callewaert *et al.* is directed to non-analogous art than Applicants' claimed invention at least because the reference discusses methods of optimizing the production of a particular endogenous protein by batch fermentation of a specific strain of a naturally occurring bacterium,

Lactobacillus amylovorus DCE 471, and not the expression of a heterologous protein. Declaration at ¶¶ 31-33. In fact, Callewaert *et al.* fails to suggest or provide motivation to a person of ordinary skill in the art to use fed-batch cultivation of any organism, other than *Lactobacillus amylovorus* DCE 471. Declaration at ¶ 34. For at least these reasons, Callewaert *et al.* does not provide motivation or suggestion to modify Madsen *et al.* in any manner. Declaration at ¶¶ 31-34.

Jensen *et al.* describes batch cultivation of *Lactococcus lactis* subsp. *lactis.*, a non-transformed bacteria, but does not teach or suggest fed-batch or continuous cultivation. See pages 4363-64; Declaration at ¶¶ 37-38. Jensen *et al.* fails to provide a motivation or suggestion to modify Madsen *et al.* to use fed-batch or continuous fermentation of any recombinant bacteria discussed by Madsen *et al.* at least because Jensen *et al.* is directed to batch cultivation of non-transformed bacteria. See also Declaration at ¶ 39. Contrary to the statement in the Office Action that Jensen's disclosure includes, "...genetically engineered strains..." (Office Action at 3), Applicants were unable to find such teaching in Jensen *et al.* If Applicants overlooked such teaching, they would appreciate the identification thereof in the publication.

The Office Action fails to establish why or how it would have been obvious to one of ordinary skill in the art at the time of the invention to combine Madsen *et al.* with Callewaert *et al.* and Jensen *et al.* to produce a method meeting all the limitations of claim 1. The Office Action also does not establish motivation to combine references nor that there is a reasonable expectation of success in combining the references. Finally, even if, *arguendo*, it were proper to combine the references, it has not been established in the Office Action that the combination would have yielded a method that meets each and every limitation of the claims.

The three fermentation systems (batch, fed-batch and continuous) are distinct and, absent an explicit teaching or a suggestion in Madsen *et al.*, it would not have been obvious to a person of ordinary skill in the art in 2000, to modify the bacterial cultivation system as taught by Madsen *et al.* to be fed-batch or continuous. Declaration at ¶¶ 14-29. The subject matter of Applicants' invention in directed to an improvement in an unpredictable art where methods developed for cultivating non-transformed bacteria and their endogenous proteins produced by such bacteria do not necessarily translate to cultivation of recombinant lactic acid bacterium, producing heterologous peptide, polypeptide, or protein. Declaration at ¶¶ 35-37.

Thus, a person of ordinary skill in the art would not have found it obvious to combine the teachings of Madsen *et al.* with Callewaert *et al.* and/or Jensen *et al.* to eliminate the batch cultivation of Madsen *et al.* and substitute therefor the fed-batch cultivation of Callewaert *et al.* at least because both Callewaert *et al.* and Jensen *et al.* are directed to cultivation of non-transformed bacteria, rather than to that of recombinant lactic acid bacterium. See also Declaration at ¶¶ 33-41.

Neither Madsen *et al.* nor any of the other references applied in this rejection suggest the desirability of modifying Madsen *et al.* and any of the improper combinations of the references would have failed to suggest to a person of ordinary skill in the art the use of fed-batch or continuous cultivation conditions in a chemically defined medium to cultivate recombinant bacterium to produce heterologous peptide, polypeptide, or protein as required by claim 1. See Declaration at ¶¶ 25-29, 39-41.

Further, dependent claims 3-10, 14, 17, 24, and 27 are directed to additional features of the invention and their patentability needs to be considered separately from that of claim 1. The Office Action does not delineate how or where each and every limitation of these dependent claims is taught or suggested by the cited references. The United States Court of Appeals for the Federal Circuit held that, "Omission of a relevant factor required by precedent is both legal error and arbitrary agency action." In re Lee, 277 F.3d 1338, 61 USPQ 2d 1430, 1434 (Fed. Cir. 2002). The court further explained that,

> "it is fundamental that rejections under 35 U.S.C. § 103 must be based on evidence comprehended by the language of that section." Quoting from *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). Id. at 1433.
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> and
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> The patent examination process centers on prior art and the analysis thereof. When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. See, e.g., *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is a reason to combine [the] references," a question of fact drawing on the *Graham* factors. Id.
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> The court continued:
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> The determination of patentability on the ground of unobviousness is ultimately one of judgment. In furtherance of the judgmental process, the patent examination procedure

> serves both to find, and to place on the official record, that which has been considered with respect to patentability. The patent examiner and the Board are deemed to have experience in the field of the invention; however, this experience, insofar as applied to the determination of patentability, must be applied from the viewpoint of "the person having ordinary skill in the art to which said subject matter pertains," the words of section 103. In finding the relevant facts, in assessing the significance of the prior art, and in making the ultimate determination of the issue of obviousness, the examiner and the Board are presumed to act from this viewpoint. Thus when they rely on what they assert to be general knowledge to negate patentability, that knowledge must be articulated and placed on the record. The failure to do so is not consistent with either effective administrative procedure or effective judicial review. The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies. Id. at 1435.

In accordance with In re Lee, it is improper for the USPTO to make a rejection under 35 U.S.C. § 103(a) by citing references and asserting that it would have been obvious to combine the references in the absence of evidence supporting the assertion that there is a teaching, motivation or suggestion to select and combine the references. To establish a *prima facie* case of obviousness of a clamed invention, the Office Action must establish that each limitation of the rejected independent and dependent claims is taught or suggested by the prior art. M.P.E.P. § 2143.03. The Office Action failed to do so at least because no evidence was presented that prior art teaches or suggests all limitations of the rejected claims.

Applicants respectfully request reconsideration and withdrawal of the rejection.

II. Claims 1-10, 14, 17, 24, and 27 are Patentable over Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, and de Vos

Claims 1-10, 14, 17, 24, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* in view of Callewaert *et al.* and Jensen *et al.* and further in view of de Vos (1999) "Gene expression systems for lactic acid bacteria." Current Opinion in Microbiology **2**: 289-295 ("de Vos"). Office Action at 4-5.

The Office Action asserted that a person of ordinary skill in the art would have found it obvious to utilize a constitutive promoter, as taught by de Vos in the method of producing heterologous protein, "...disclosed by Madsen et al., in view of Callewert et al. and Jensen since the references disclose...use of promoters operably linked to a gene encoding a polypeptide..." Id. at 5.

Applicants respectfully traverse this rejection.

As discussed above, Madsen *et al.* does not discuss or suggest fed-batch or continuous cultivation systems, and fails to provide a suggestion or motivation to substitute a fed-batch or continuous cultivation process for the batch cultivation method taught by him. See also Declaration at ¶¶ 42-44. Also as discussed above, Callewaert *et al.* teaches or suggests fed-batch cultivation of *Lactobacillus amylovorous*, to produce an endogenous protein, amylovorin L471. Jensen *et al.* teaches batch cultivation of non-transformed bacteria, *Lactococcus lactis* subsp. *lactis*. Declaration at ¶¶ 44-45

As also discussed above, Madsen *et al.*, Callewaert *et al.* and Jensen *et al.*, would have failed to suggest to a person of ordinary skill in the art the combination of the three disclosures, and any possible combination would have failed to suggest the method of claim 1. See also Declaration at ¶ 45.

de Vos describes gene expression systems for lactic acid bacteria, such as constitutive and inducible, but does not teach or suggest fed-batch or continuous cultivation. Declaration at ¶¶ 46-47. Further, de Vos fails to provide motivation or suggestion to modify Madsen *et al.* (alone or with the other references discussed in this rejection) in any manner. In particular, de Vos contains no suggestion or motivation to use fed-batch or continuous cultivation of any organism. Declaration at ¶¶ 46-48.

The Office Action also does not establish motivation to combine the four references nor that there is a reasonable expectation of success in combining them. Finally, even if, *arguendo*, it were proper to combine the references, it has not been established in the Office Action that the combination would have yielded a method that meets each and every limitation of claim 1, and the dependent claims. Declaration at ¶¶ 15-21, 29, 35-38, 47, 48.

Thus, a person of ordinary skill in the art would not have found it obvious to combine the teachings of Madsen *et al.* with Callewaert *et al.*, Jensen *et al.* and de Vos to eliminate the batch cultivation of Madsen *et al.* and substitute therefor the fed-batch cultivation of Callewaert *et al.* at least because both Callewaert *et al.* and Jensen *et al.* are directed to cultivation of non-transformed bacteria, and neither Madsen *et al.*, Jensen *et al.*, nor de Vos teach or suggest fed-batch or continuous cultivation. See also Declaration at ¶¶ 34, 39-41. Nor would it be obvious to use the gene expression systems of de Vos in any of the preceding combinations. Declaration at ¶¶ 46-47.

Further, dependent claims 2-10, 14, 17, 24, and 27 are directed to additional features of the invention and their patentability needs to be considered separately from that of claim 1. While claim 2 recites a constitutive promoter, this claim is dependent from claim 1. Since claim 1 is not obvious for the reasons discussed above, claim 2 is also patentable in view of the same references.

The Office Action does not establish how each and every limitation of these dependent claims is taught or suggested by the cited references. Instead, the Office Action asserts that, "One [of ordinary skill in the art] would have been motivated to do so by the well known properties of constitutive promoters...as disclosed by de Vos." Office Action at 5. The Office Action must establish a teaching or suggestion in prior art for each and every limitation of the independent and dependent claims. In re Lee, and M.P.E.P. § 2143.03 *supra*. It failed to do so.

Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Claims 1-11, 14, 17, 24, and 27 are Patentable over Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, and van Asseldonk *et al.*

Claims 1-11, 14, 17, 24, and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* in view of Callewaert *et al.* and Jensen *et al.* and in further view of van Asseldonk *et al.* (March 1993) "Cloning, Nucleotide Sequence, and Regulatory Analysis of the *Lactococcus lactis dnaJ* Gene." Journal of Bacteriology **175**(6): 1637-1644 ("van Asseldonk *et al.*"). Office Action at 5-6.

The Office Action stated that Madsen *et al.* and Jensen *et al.* were cited for the reasons discussed in previous rejections and the difference between the references and the, "...instant claim is that a particular signal peptide, i.e., the usp45 is utilized". Id. van Asseldonk *et al.* was cited for its disclosure of the usp45 signal peptide and its use in producing a protein in *L. lactis*. Id.

As discussed herein, Madsen *et al.* does not discuss or suggest fed-batch or continuous cultivation systems, and fails to provide any suggestion or motivation to do so. Further, Callewaert *et al.* teaches fed-batch cultivation and suggests results thereof "are interesting regarding the development of continuous fermentation" of one bacterial strain, *Lactobacillus amylovorous* DCE 471 to produce an endogenous protein, amylovorin L471. Declaration at

¶¶ 31, 49-50. And, as discussed above, Jensen *et al.* only teaches batch cultivation of non-transformed bacteria, *Lactococcus lactis* subsp. *lactis*. For the reasons discussed in detail *supra*, Madsen *et al.*, Callewaert *et al.* and Jensen *et al.* would not have suggested to a person of ordinary skill in the technology of this application the combination of disclosures of these three references. Applicants also pointed out above that any possible combination would not have suggested the method of claim 1. Declaration at ¶ 50.

van Asseldonk *et al.* does not teach or suggest fed-batch or continuous cultivation nor provides a motivation or suggestion to modify Madsen *et al.* alone, or when combined with Callewaert *et al.* and Jensen *et al.* in any manner. In particular, van Asseldonk *et al.* fails to provide a suggestion or motivation to use fed-batch or continuous cultivation of any organism at least because van Asseldonk *et al.* describes batch and plate-based cultivation. Declaration at ¶¶ 51-52.

The Office Action also does not establish motivation in the references to combine them nor that there is a reasonable expectation of success in combining the references. Even if, *arguendo*, it were proper to combine Madsen *et al.* with Callewaert *et al.*, Jensen *et al.*, and van Asseldonk *et al.* the combination would not have suggested to a person of ordinary skill in the art the invention of claim 1, at least because the combination would have failed to include or suggest the use of fed-batch or continuous cultivation of recombinant bacteria in the context of producing a heterologous peptide, polypeptide, or protein, as defined in claim 1. Declaration at ¶¶ 52-53. Nor would it have been obvious to use the *usp45-amyS* secretion cassette of van Asseldonk *et al.* in any of the preceding combinations.

Further, dependent claims 2-11, 14, 17, 24, and 27 are directed to additional features of the invention and their patentability must be considered independently of claim 1. The Office Action does not establish how each and every limitation of these dependent claims is taught or suggested by the cited references. Instead, the Office Action asserts that:

> It would have been obvious to one of ordinary skill in the art, to have utilized a known L lactis signal peptide such as the usp45 signal peptide, in the method of producing heterologous protein disclosed by Madsen *et al.* and Jensen *et al.*, since both references disclose methods of expression of genes in lactic acid bacteria, including the use of signal peptides operably linked to a gene encoding a polypeptide whose expression is desired. Office Action at 6.

While claim 11 includes usp45 as a possible signal peptide, van Asseldonk *et al.*'s disclosure of that signal peptide fails to render obvious claim 11 at least because van Asseldonk

et al. does not disclose or suggest fed-batch or continuous cultivation of a recombinant lactic acid bacteria to produce heterelogous peptide, polypeptide or protein, as defined in claim 11, which is dependent from claim 1. The Patent Office bears the burden of establishing a *prima facie* case of obviousness for each and every limitation of the independent and dependent claims. In re Lee, and M.P.E.P. § 2143.03, *supra*. The Office Action failed to meet this burden

Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. Claims 30, 32-39, and 41-45 are Patentable over Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.*

Claims 30, 32-39, and 41-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* in view of Callewaert *et al.* and Jensen *et al.* and further in view of Israelsen *et al.* (July 1995) "Cloning and partial characterization of regulated promoters from *Lactococcus lactis* Tn917-lacZ integrants with the new promoter probe vector, pAK80." Applied and Environmental Microbiology **61**(7): 2540-2547. ("Israelsen *et al.*") Office Action at 6-9.

The rejection is based on the characterization of Madsen *et al.*'s disclosure similar to that in the first rejection (i.e., the rejection of claims 1, 3-10, 14, 17, 24 and 27 under 35 U.S.C. § 103(a) over Madsen *et al.* in view of Callewaert *et al.* and Jensen *et al.* at pages 2-4 of the Office Action). It was also asserted, in pertinent part, that Israelsen *et al.* teaches a method of making a heterologous protein with recombinant lactic acid bacteria, utilizing the culture medium supplemented with yeast and glucose. Office Action at 6-9.

Applicants respectfully traverse this rejection.

Claim 30 is the only independent claim in this rejection, and the remaining rejected claims are dependent from claim 30. One substantive difference between claim 30 and claim 1 is that claim 30 requires the chemically defined medium to be supplemented with yeast extract.

Claim 30, considered as a whole, is not rendered obvious by Madsen *et al.*, Callewaert *et al.*, Jensen *et al.* and Israelsen *et al.*, for the reasons discussed below. For at least this reason, the remaining rejected claims which depend from claim 30, are also patentable in view of these references.

As discussed above, Madsen *et al.* does not discuss or suggest fed-batch or continuous cultivation systems, and fails to provide a suggestion or motivation to substitute a fed-batch or continuous cultivation process for the batch cultivation method taught by him. See also

Declaration at ¶ 55. Also as discussed above, Callewaert *et al.* discloses fed-batch cultivation of one bacterial strain, *Lactobacillus amylovorous* DCE 471, and suggests that results thereof may be interesting with regard to developing continuous fermentation processes for that bacterial strain to produce one endogenous protein, amylovorin L471. See also Declaration at ¶¶ 31-32. Further, Jensen *et al.* does not provide motivation or suggestion to modify Madsen *et al.* in any manner. See also Declaration at ¶¶ 38-39.

Israelsen *et al.* does not teach fed-batch or continuous cultivation nor provide any motivation or suggestion to modify Madsen *et al.*, or to combine Madsen *et al.*, Callewaert *et al.* and Jensen *et al.* in any manner. In particular, Israelsen *et al.* does not provide any suggestion or motivation to use fed-batch or continuous cultivation of any organism. Declaration at ¶¶ 56-58.

Neither Madsen *et al.* nor any of the other references applied in this rejection suggest the desirability of modifying Madsen *et al.* and any of the combinations of the references would have failed to suggest to a person of ordinary skill in the art the use of fed-batch or continuous cultivation conditions in a chemically defined medium to cultivate recombinant bacterium to produce heterologous peptide, polypeptide, or protein as required by claim 30. See Declaration at ¶ 58.

For the reasons discussed above, the combination of Madsen *et al.*, Callewaert *et al.* and Jensen *et al.* is not warranted by their disclosures. There is no motivation or suggestion in these three disclosures nor in Israelsen *et al.* to combine the four references, at least because the references are directed to disparate aspects of bacteria cultivation. For example, Madsen *et al.* describes batch cultivation of recombinant bacteria, Callewaert *et al.* fed-batch cultivation of a particular, non-transformed bacterial strain, Jensen *et al.* teaches batch cultivation of *Lactococcus lactis* subsp. lactis, a non-transformed bacteria, and Israelsen *et al.* is directed to the construction of *Lactococcus lactis* Tu917-LTV1 integrants expressing β-galactactosidase, and uses batch cultivation. There is simply no suggestion or motivation in the disclosures of these references to combine them. The Office Action fails to establish why or how it would have been obvious to one of ordinary skill in the art at the time of the invention to combine Madsen *et al.* with Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.* to produce a method meeting all the limitations of claim 30. Even if, *arguendo*, it were proper to combine the references, it has not been established in the Office Action that the combination would have yielded a method that meets each and every limitation of claim 30. Declaration at ¶¶ 55-58.

Further, dependent claims 32-39 and 41-45 are directed to additional features of the invention and their patentability must be considered separately from that of claim 30. The Office Action does not establish how each and every limitation of these dependent claims is taught or suggested by the cited references. Instead, the Office Action asserts that, "One would have been motivated to do so by the well known advantages of using growth medium containing yeast extract, which include the ability to cultivate to high levels lactic acid bacteria such as L. lactis, as disclosed by the references." Office Action at 8-9. As discussed previously, the USPTO must establish a *prima facie* case of obviousness for each and every limitation of the independent and dependent claims. In re Lee, and M.P.E.P. § 2143.03, *supra*. The Office Action failed to do so.

Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Claims 30-39 and 41-45 are Patentable over Madsen *et al.*, Callewaert *et al.*, Israelsen *et al.*, and de Vos

Claims 30-39 and 41-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* in view of Callewaert *et al.*, Jensen *et al.* and Israelsen *et al.* and further in view of de Vos. Office Action at 9-10.

The Office Action reiterated the citation of Madsen *et al.*, Callewaert *et al.*, Jensen *et al.* and Israelsen *et al.*, for the previously-cited reasons. The asserted difference between the rejected claims and the references was the use of a constitutive promoter. de Vos was relied upon for its disclosure of constitutive promoters "...for the expression of genes in lactic acid bacteria." Office Action at 9. It was concluded that a person of ordinary skill in the art would have found it obvious to have utilized a constitutive promoter "...taught by de Vos, in the method of producing heterologous protein disclosed by Madsen *et al.* in view of Jensen and Israelsen, since references disclose methods of expression of genes in lactic acid bacteria, including the use of promoters linked to a gene encoding a polypeptide whose expression is desired." Id. at 9-10. Applicants respectfully traverse this rejection.

Neither Madsen *et al.* nor any of the other references applied in this rejection suggest the desirability of modifying Madsen *et al.* and any of the combinations of the references would have failed to suggest to a person of ordinary skill in the art the use of fed-batch or continuous cultivation conditions in a chemically defined medium to cultivate recombinant bacterium to

produce heterologous peptide, polypeptide, or protein as required by claim 30. See Declaration at ¶¶ 26-30, 59-63.

For the reasons discussed above, the combination of Madsen *et al.*, Callewaert *et al.*, Jensen *et al.* and Israelsen *et al.*, is not warranted by their disclosures. See also Declaration at ¶¶ 56-57. Further, as established above, any combination of Madsen *et al.* with Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.*, would not have suggested to a person of ordinary skill in the art the invention of claim 30. In addition, de Vos' disclosure fails to supply the motivation to combine it with the former four references. Declaration at ¶ 62. Any combination of Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.*, and de Vos would have failed to render *prima facie* claim 30 obvious to a person ordinarily skilled in the art at least because the combination would have failed to include or suggest the use of fed-batch or continuous cultivation of recombinant bacteria to produce a heterologous peptide, polypeptide, or protein, as defined in claim 30. Declaration at ¶ 63.

Thus, contrary to the assertion in the Office Action, a person of ordinary skill in the art would not have found it obvious to combine the teachings of the five references to eliminate the batch cultivation of Madsen *et al.* and substitute therefor the fed-batch cultivation of Callewaert *et al.* at least because both Callewaert *et al.* and Jensen *et al.* are directed to cultivation of non-transformed bacteria, rather than to that of recombinant lactic acid bacterium. See Declaration at ¶¶ 60-62.

Further, dependent claims 31-39 and 41-45 are directed to additional features of the invention and their patentability must to be determined in view of such additional features. Claim 31 recites the presence of a constitutive promoter in the recombinant bacterium. Since this claim depends from claim 30, it includes all the limitations of claim 30 (in addition to the constitutive promoter required by claim 31). de Vos' disclosure of the constitutive promoter does not render obvious claim 30. Thus, claim 31 is also patentable in view of Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, Israelsen *et al.* and de Vos, at least because the albeit improper combination of these references would have failed to suggest fed-batch or continuous cultivation of recombinant lactic acid bacterium.

The Office Action does not establish how each and every limitation of dependent claims is taught by the cited references. Instead, the Office Action asserts that:

> It would have been obvious to one of ordinary skill in the art, to have utilized a constitutive promoter as taught by deVos, in the method of producing heterologous protein disclosed by Madsen, et al. in view of Jensen and Israelsen, since the references disclose methods of expression of genes in lactic acid bacteria, including the use of promoters operably linked to a gene encoding a polypeptide whose expression is desired.
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> and
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> One would have been motivated to do so by the well known properties of constitutive promoters, which include high levels or production of an operably linked gene of interest, as disclosed by de Vos.
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> Office Action at 9-10.

The USPTO must establish that prior art teaches or suggests all claim limitations of each dependent and independent claim, In re Lee, and M.P.E.P. §2143.03, *supra*. The Office Action failed to do so.

Applicants respectfully request reconsideration and withdrawal of the rejection.

VI. Claims 30-45 are Patentable over Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, Israelsen *et al.*, and van Asseldonk *et al.*

Claims 30-45 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Madsen *et al.* in view of Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.* and further in view of van Asseldonk *et al.* Office Action at 10-11.

Madsen *et al.*, Callewaert *et al.*, Jensen *et al.*, and Israelsen *et al.* were cited for, "...the reasons set forth above." Office Action at 10. The Office Action asserted that the difference between the references and "...the instant claim..." is the use of a particular signal peptide, the usp45. Since van Asseldonk *et al.* assertedly discloses such signal peptide, and its use in producing protein in *L. lactis,* it was asserted that one of ordinary skill in the art would have found it obvious to use a known *L. lactis* signal peptide, such as usp45, in the method of Madsen *et al.* and Jensen *et al.* Id.

Applicants respectfully traverse this rejection.

Neither Madsen *et al.* nor any of the other references applied in this rejection suggest the desirability of modifying Madsen *et al.* and any of the combinations of the references would have failed to suggest to a person of ordinary skill in the art the use of fed-batch or continuous cultivation conditions in a chemically defined medium to cultivate recombinant bacterium to

produce heterologous peptide, polypeptide, or protein as required by claim 30. See Declaration at ¶¶ 64-69.

For the reasons discussed above, the combination of Madsen *et al.*, Callewaert *et al.*, Jensen *et al.* and Israelsen *et al.*, is not warranted by their disclosures. Also see Declaration at ¶¶ 56-57. van Asseldonk *et al.*'s teaching of the *dnaJ* gene and batch and plate-based cultivations fail to provide a motivation to combine with this reference the first four references used in this rejection. Any, albeit improper, combination of Madsen *et al.* with Callewaert *et al.*, Jensen *et al.*, Israelsen *et al.*, and van Asseldonk *et al.* would not have suggested to a person of ordinary skill in the art the invention of claim 30, at least because the combination would have failed to include or suggest the use of fed-batch or continuous cultivation of recombinant bacteria to produce a heterologous peptide, polypeptide, or protein, as defined in claim 30. Declaration at ¶¶ 68-69.

Thus, a person of ordinary skill in the art would not have found it obvious to combine the teachings of Madsen *et al.* with Callewaert *et al.*, Jensen *et al.*, Israelsen *et al.*, and van Asseldonk *et al.*, to eliminate the batch cultivation of Madsen *et al.* and substitute therefor the fed-batch cultivation of Callewaert *et al.* at least because both Callewaert *et al.* and Jensen *et al.* are directed to cultivation of non-transformed bacteria, rather than to that of recombinant lactic acid bacterium. See also Declaration at ¶¶ 64-66. Nor would it have been obvious to use the culture media of Israelsen *et al.* in any of the preceding combinations or the *usp45-amyS* secretion cassette of van Asseldonk *et al.* in any of the preceding combinations. Declaration at ¶¶ 56-57, 66-68.

Further, dependent claims 31-45 are directed to additional features of the invention and their patentability needs to be considered separately from that of claim 30, and in light of such additional claimed features. The Office Action does not establish how or where each and every limitation of these dependent claims is taught or suggested by the cited references. While claim 40 recites Usp45 as a possible signal peptide, this does not render claim 40 obvious, at least because van Asseldonk *et al.*, and the remaining references relied upon in this rejection, fail to teach or suggest fed-batch or continuous cultivation conditions for recombinant lactic acid bacteria to produce heterelogous peptide, polypeptide or protein, as defined in claim 30, and thus in claim 40. Instead, the Office Action asserts that:

> It would have been obvious to one of ordinary skill in the art, to have utilized a known L. lactis signal peptide such as the usp45 signal peptide, in the method of producing heterologous protein disclosed by Madsen et al. and Jensen et al., since both references disclose methods of expression of genes in lactic acid bacteria, including the use of signal peptides operably linked to a gene encoding a polypeptide whose expression is desired.
>
> and
>
> One would have been motivated to do so by the well known property of the usp45 signal peptide in directing the secretion of a heterologous protein from a lactic acid bacteria, as disclosed by van Asseldonk et al.
> Office Action at 10-11.

Again, the Office Action fails to establish how the prior art teaches or suggests all claim limitations of the independent and dependent claims. In re Lee and M.P.E.P.§ 2143.03, *supra.*

Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Unexpected Results Overcome Any Possible *prima facie* Case of Obviousness.

Even if, *arguendo*, *prima facie* obviousness were established by the combined references, the unexpected results found by the inventors using fed-batch or continuous fermentation processes to produce a heterologous peptide, polypeptide, or protein in a lactic acid bacterium host cell would rebut that *prima facie* case. The inventors found that using batch fermentation with chemically defined media produced a significantly lower yield than using batch fermentation with a conventional undefined media. Specification at 4 lines 4-11; Example 8; Table 2. The inventors found that this problem was overcome, surprisingly, by changing the fermentation method to fed-batch or continuous. Declaration at ¶ 22. In addition, the continuous fermentation process produces less product per hour but has a higher overall yield because it can be run for longer periods of time. Specification at Example 8; Table 2. Neither of these factors are taught by any of the references cited in the Office Action. Declaration at ¶¶ 15-20.

Claim Rejections 35 U.S.C. 112

Claims 6 and 35 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards at the invention.

The limitation P170 promoter or a derivative thereof is taught in the specification to be pH inducible, where the P170 promoter is induced by low pH. Specification at 3 lines 10-20; 4 lines 31-33; 8 lines 22 to 9 line 19. The productivity and kinetics of the P170 expression system is taught in the Specification at Example 3 and examples using it are taught at Example 4-7 of the specification. Therefore the metes and bounds of the limitation are clearly delineated in the specification, as will be apparent to one of ordinary skill in the art.

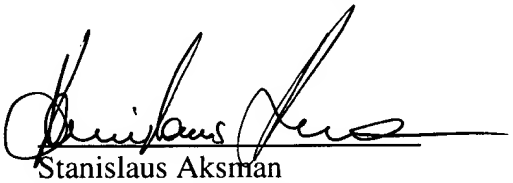
Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that the application is in condition for allowance and respectfully request a notice of allowance for the pending claims. Should the Examiner determine that any further action is necessary to place this application in condition for allowance, the Examiner is kindly requested and encouraged to telephone Applicants' undersigned representative at the number listed below.

It is believed that no additional fee is due in connection with this filing. However, in the event that any fees are necessary, the Commissioner is hereby authorized to charge our **Deposit Account No. 50-0206**.

Respectfully submitted,
HUNTON & WILLIAMS LLP

Date: April 5, 2006 By: 

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